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Activated Recombinant Human Coagulation Factor VII (rFVIIa) Therapy for Abdominal Bleeding in Patients With Inhibitory Antibodies to Factor VIII

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Eight patients with inhibitors to factor VIII (4 hemophilia A and 4 nonhemophilic) were treated with recombinant activated factor VII (rFVIIa) to control severe abdominal bleeding. The recombinant factor was supplied under an open-label, emergency-use program to patients previously unresponsive to one or more alternative therapies. Therapy with rFVIIa was administered for nine separate bleeding events; one patient was treated for two separate bleeding episodes. Patients were treated for an average of 9 days and received a mean total dose of 5.2 mg of rFVIIa for control of bleeding. Treatment was considered successful and hemostasis adequate in 7 of the 9 episodes (78%). Treatment with rFVIIa was partially successful in one other episode. Four patients in this series experienced serious adverse events; all the adverse events were considered unrelated to rFVIIa therapy. The results of this limited series indicate that rFVIIa is an effective means of managing life-threatening abdominal bleeding in individuals with hemophilia or acquired antibodies to factor VIII. Am. J. Hematol. 63:109–113, 2000. © 2000 Wiley-Liss, Inc.

Key words: recombinant factor VIIa; hemostasis; abdominal bleeding; hemophilia A; acquired antibodies

INTRODUCTION

Clinical management of abdominal bleeding is difficult under any circumstances, but in patients with inhibitory antibodies to factor VIII due to hemophilia A or to idiopathic acquired antibodies to factor VIII, it poses significant problems. Until recently, bleeding from any site in hemophiliac patients with inhibitors to factor VIII indicated a bleak prognosis [1,2]. Restoration of hemostatic capability with concentrates of purified human or porcine factor VIII is one option [3,4], but in patients with acquired antibodies the infused factors are rapidly inactivated. Prothrombin complex concentrate (PCC) or activated prothrombin complex concentrates (aPCC) that bypass factor VIII are effective in approximately half of treated bleeding episodes but often cause thromboembolic complications [2,4,5–7].

Activated factor VII can also bypass functional deficiencies of factor VIII or IX in hemophilia A or B, respectively. Recombinant activated factor VII (rFVIIa), like its native counterpart, is hemostatically active when complexed with tissue factor (TF) at sites of vessel injury and, when given in pharmacologic doses, can directly activate factor X independent of tissue factor [8]. Several clinical studies have established the clinical efficacy of rFVIIa for control of bleeding from various sites in individuals with inhibitors to factor VIII or factor IX due to hemophilia A or B and in patients with idiopathic acquired inhibitory antibodies to factor VIII [7,9–15]. Re-

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combinant activated factor VII has also been shown to be effective and safe in patients with factor inhibitors undergoing surgery [9,11,16].

Recently, rFVIIa has been used (NovoSeven, Novo Nordisk Pharmaceuticals Inc., Princeton, NJ) in an open-label, emergency-use program to control spontaneous or surgically induced abdominal bleeding episodes in patients with acquired antibodies to factor VIII. This report summarizes the results of a limited trial in which rFVIIa was administered to patients who required acute treatment of abdominal hemorrhage.

MATERIAL AND METHODS

Patients

Patients enrolled in this open-label, uncontrolled, emergency-use program were required to have one of the following conditions: severe hemophilia A (factor VIII <1%) or B (factor IX <1%), acquired antibodies to factor VIII or IX, or a deficiency of factor VII (less than 5%) with no alternative therapy available. In addition, eligibility for therapy with rFVIIa required risk of a life-threatening abdominal bleeding episode that was unresponsive to alternative therapy or therapies (e.g., factor VIII, factor IX, porcine factor VIII, PCC/aPCC, or fresh frozen plasma). In this series, all eight individuals were at risk for extensive abdominal bleeding. All patients or their guardians provided informed consent before initiation of treatment. The institutional review board at each participating institution approved the emergency-use protocol.

Procedures

rFVIIa was reconstituted in sterile water immediately before use. Patients received intravenous bolus injections (90 μg/kg body weight) of rFVIIa every 2 hr. If no clinical improvement was apparent, the dose could be increased to a maximum of 120 μg/kg body weight at the physician's discretion. If bleeding was controlled but continued therapy was indicated, the dosing interval was increased to 3–4 hr for as long as treatment was indicated.

Efficacy was determined by the hemostatic response to rFVIIa at the end of the treatment period. Treatment was classified by the attending physician as effective (complete or substantial decrease in hemorrhage), partially effective (some decrease in hemorrhage), or ineffective (no improvement in hemorrhage). Patients were closely monitored for signs and symptoms of disseminated intravascular coagulation or hypersensitivity reactions. Patients who were considered at risk of adverse coagulation-related events were also monitored for activation of the coagulation system. However, due to the institutional differences in monitoring patients for hemostatic activation, no consistent data set is available for all patients.

RESULTS

Eight patients were treated with rFVIIa for emergency control of a life-threatening abdominal hemorrhage. Four individuals had severe hemophilia A with inhibitors to FVIII, and four had acquired antibodies to FVIII (Table I). In this series, rFVIIa was used in nine separate, emergency hemorrhages where bleeding was situated in the abdomen (2 retroperitoneal, 4 gastrointestinal, and 3 intra-abdominal). One patient was treated for two separate retroperitoneal bleeds; all others were treated once. Two individuals were treated for bleeding related to post-surgical events, and four others were treated for gastrointestinal bleeding; one patient also experienced left pleural effusion and bleeding into the thigh. Prior to the administration of rFVIIa, all patients had failed therapy with numerous agents and had experienced bleeding episodes lasting from 2 to 18 days (Table I).

The duration of treatment for all patients in the series ranged from 4 to 20 days, with a mean of 9 days. Patients with hemophilia A were treated for a mean of 7.2 days (range = 4–12), and those with acquired antibodies were treated for a mean of 11.3 days (range = 7–20). The total dose of rFVIIa for all patients ranged from 2.2 to16.4 mg with a mean of 5.2 mg (SD = 3.3). These data are summarized in Table I.

Of nine treatment episodes, bleeding was effectively controlled in seven (78%) hemorrhages, including all four hemophilia A patients and two patients with acquired antibodies. Hemorrhage was partially controlled in one (11%) episode in a patient with acquired antibodies. Efficacy could not be assessed in one patient (11%) who died as a result of unrelated complications. None of the patients had clinical evidence suggestive of disseminated intravascular coagulation. No patient developed thrombocytopenia associated with rFVIIa therapy. Patient HS had a fibrinogen that decreased slightly from 281 to 254 mg/dl during rFVIIa therapy, with an increase in fibrin split products from 5–20 to >20 mcg/ml. Patient JZ had an elevated fibrinogen of 387 mg/dl at the end of rFVIIa therapy with concomitant elevations in the D-dimer of 500–1000 ng/ml. However, his protamine paracoagulation test for fibrin monomer was negative. The D-dimer elevations were believed to be secondary to extensive intramuscular and intra-abdominal bleeding.

Three of the eight patients experienced severe adverse events that resulted in death during treatment (Table II). All three of these patients had acquired antibodies to factor VIII. Serious adverse events that resulted in death included hypotension leading to shock, cerebrovascular disorder with subsequent thrombophlebitis and pulmonary embolism, respiratory failure, and intracranial hemorrhage. In all three cases, the serious adverse events were judged by the responsible investigator to be results of underlying disease and unrelated to therapy with

TABLE I. Demographics and Diagnosis for Individuals Treated With rFVIIa for Abdominal Bleeding

Diagnosis/ patient	Age (y), Sex, Race[a]	Weight (kg)	Inhibitory titers[a] (BU)	Previous therapies	Duration of bleeding episode (days)	No. of injections[b]	No. of days treated	Total dose (mg/kg)	Outcome
Hemophilia A									
RI	35, M, B	130	Un	Porcine FVIII, FEIBA, IgG, DDAVP	18	37	8	3.3	Effective
						77	12	6.4	Effective
MJL	10, M, Un	35	Human: 33 Porcine: 14	FIX, porcine FVIII aPCC/PCC, corticosteroids	2	35	7	3.2	Effective
HS	25, M, B	61	Human: 880 Porcine: 420	Porcine FVIII aPCC/PCC, corticosteroids	5	31	5	2.4	Effective
KJB	25, M, B	54	Human: 4089 Porcine: 727	Antifibrinolytics	6	25	4	2.2	Effective
Acquired antibodies									
CC	82, M, B	52	Human: 16	FVIII, procine FVIII, aPCC/PCC, corticosteroids, fresh frozen plasma	14	163	20	16.4	Effective
JZ	79, M, W	104	Human: 13 Porcine: 3	FVIII, porcine FVIII aPCC/PCC, corticosteroids, IgG, antifibrinolytics, cytostatics, fresh frozen plasma	4	35	9	3.2	Effective
AO	62, M, H	66	Human: 15	APCC/PCC	2	69	9	6.5	Partially effective
			Porcine: 4	corticosteroids, cytostatics, fresh frozen plasma					
HD	51, F, AA/NAm	72	Human: 36	FVIII, FIX, porcine FVIII, corticosteroids, IgG, cytostatics	14	40	7	3.3	Died

[a]M = male; F = female; B = Black; Un = Unknown; W = White; His = Hispanic; AA/NAm = African American/Native American; BU = Bethesda units.
[b]rFVIIa was injected at a dosage of 90 μg/kg body weight and repeated every 2 hr until bleeding was controlled.

TABLE II. Serious Adverse Events in Three Patients With Acquired Antibodies During Treatment With rFVIIa

Patient	Explanation	Related to rVIIa
C.C.	Cerebrovascular disorder, thrombophlebitis, pulmonary emoboli, supraventricular tachycardia, aspiration pneumonitis, death	Unlikely, possible contributing factor
A.O.	Respiratory failure, death	Unlikely
H.D.	Immunoinflammatory disease, thrombotic stroke, intracranial hemorrhage, death	Unlikely

rfVIIa. In the case of patient HD, however, the outcome may have been the result of a reduced therapeutic response.

Patient CC, an 85-year-old man with a history of rheumatoid arthritis and diabetes mellitus, developed severe gastrointestinal bleeding after surgical correction of a hip fracture. He was treated with factor VIII concentrates, porcine factor VIII, fresh frozen plasma, and aPCC/PCC without control of his bleeding. rFVIIa was then administered with frozen fresh plasma and corticosteroids. Treatment with rFVIIa resulted in control of bleeding, but the patient subsequently developed a proximal venous thrombosis and treatment with rFVIIa was stopped. Because thrombophlebitis is a well-known complication of hip surgery, the responsible investigator reported the serious adverse events as unrelated to the administration of rFVIIa. The complex nature of this patient's medical condition and the concurrent administration of multiple hemostatic agents confuse any clear assessment of the relationship of this event with the administration of rFVIIa.

DISCUSSION

Management of abdominal bleeding in patients with hemophilia and acquired antibodies to factor VIII or IX remains a difficult clinical problem. rFVIIa is a new therapy that bypasses steps in the coagulation cascade inhibited by the lack of active coagulation factor VIII or IX and provides an effective and potentially safer treatment for patients with inhibitory antibodies.

Several characteristics of rFVIIa may offer advantages over previously used and more conventional therapies. It produces a local hemostasis in those individuals with

hemophilia who lack active factor VIII or IX, and it avoids potential complications for those who have developed antibodies to those factors [9,11,13]. Because it is thought that rFVIIa forms a complex with TF to become enzymatically active, thereby bypassing the coagulation cascade, it produces hemostasis only at sites of injury and reduces the risk of thromboembolic complications [7,11,14]. However, recent studies suggest that the bypassing activity of high-dose rFVIIa is independent of TF and may directly activate factor Xa, which associates with activated platelets that accumulate at the site of vessel injury, resulting in localized thrombin generation [8,17]. The TF bypassing activity of high-dose rFVIIa may be clinically significance since continuous infusion rFVIIa appears to be much less efficacious in controlling bleeding then bolus injections of the factor [18].

rFVIIa is derived from cultured cells rather than from human plasma, which obviates the expense of large quantities of purified factor and reduces the risk of contamination with either human viruses or other coagulation factors [4]. Finally, data acquired to date indicate that rFVIIa lacks antigenicity, and it can be used repeatedly without loss of efficacy in patients who have inhibitory antibodies to other coagulation factors [10].

There is a growing body of clinical experience with rFVIIa that documents its efficacy and safety. Various small studies and case reports indicate that rFVIIa is both safe and effective for control of mild-to-moderate and severe bleeding episodes in individuals with hemophilia and inhibitors to FVIII [10]. Hedner and Glazer [4] reported successful rFVIIa treatment of retroperitoneal bleeds in eight patients, one of whom subsequently experienced a fatal rebleed after withdrawal of the factor. None of the other patients presented in this report experienced serious adverse effects, and all showed significant clinical improvement within 24 hr of treatment [4].

Similar results were observed in this study of patients with hemophilia A or acquired antibodies treated with rFVIIa for abdominal bleeding. rFVIIa produced effective hemostasis in 7 of 9 (78%) separate, severe, life-threatening abdominal hemorrhages, and it was partially effective in an additional episode. All patients were previously unresponsive to one or more alternative therapies.

Although three of the patients in our series experienced severe adverse events that resulted in death while they were being treated with rFVIIa, none of the events were judged to be the result of rFVIIa administration. All patients enrolled in this emergency-use program were seriously ill, had complex medical problems, and had failed multiple therapies to control bleeding. All three patients who experienced serious adverse effects had idiopathic acquired inhibitory antibodies to factor VIII. Green and Lechner [1], in their survey of 215 nonhemophilic patients with inhibitors to factor VIII, reported a 22% mortality in their patients, with uncontrolled bleeding contributing to the majority of deaths. The four patients with acquired antibodies reported on in this study are typical of these patients, who would most likely die either directly or indirectly due to uncontrolled bleeding. The fact that bleeding was controlled in two of our patients and that one patient (J.Z.) survived with subsequent elimination of his antibody strongly suggest that rFVIIa may represent an important new therapeutic agent for the treatment of bleeding in patients with idiopathic acquired antibodies to factor VIII.

On the basis of observations of this small series of patients and a previous report, we conclude that rFVIIa is an effective therapeutic agent for the control of severe abdominal hemorrhage in individuals with hemophilia A or acquired antibodies to factor VIII, particularly where other means of treatment have failed [4]. NovoSeven is now available for the treatment of active bleeding in patients with factor VIII or factor IX inhibitory antibodies. However, the optimum dose or dosing regimen for treatment depending on the type and severity of the hemorrhage remains to be determined.

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